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MARSCHEL, A

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☒ This application has been examined ☒ Responsive to communication filed on 4/28/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 10-19, 51-53, and 127-130 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-9, 20-50, 54-126 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 10-19, 51-53, and 127-130 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____ .

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

Applicants' amendments filed 4/28/93 have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-12, 17-19, 51-53, and 127-130 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to staining methods that detect BCR-ABL fusion as the method of detection of CML diagnostic mutations. CML diagnosis based on said fusion is disclosed in the specification at page 14, lines 21-25. No other genetic rearrangement that is diagnostic for CML is instantly disclosed. It is noted that claim 10, for example, is directed to CML diagnosis in lines 6-9. The claimed method steps in claim 10, however, do not contain a single step that is limited to BCR-ABL fusion detection but instead are exceedingly broad in that they are directed to hybridization practice between a mixture of labeled nucleic acid fragments undefined as to genomic target. The 35 kb complexity does not limit the target to any genomic

region and therefore fails to direct the claim practice to CML detection. Claim 12 cites breakpoints but these also lack enablement as to CML diagnosis in that said citation from page 14 states that BCR-ABL fusion "ususally" involves this translocation. This is an admission that BCR-ABL fusion is diagnostic and not the breakpoint rearrangements cited in claim 12. In summary, the scope of claim 10 and the other claims listed as rejected above is exceedingly broad and far beyond CML detection practice which is enabled instantly only regarding BCR-ABL fusion detection. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Claims 10-19, 51-53, and 127-130 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 and claims dependent therefrom are vague and indefinite in that line 9 states that the claimed method is diagnostic for CML whereas, in contrast, claim 10 lacks any step that accomplishes CML diagnosis. For example, the last two lines of claim 10 practices the visualization of hybridized labeled fragments but lacks any CML diagnostic practice. CML diagnosis requires more than simple visualization. For example, there must be some diagnostic distinction or pattern that is recognizable from the visualized nucleic acids. Stated in another way, what visual pattern is diagnostic for CML versus the pattern that is not diagnostic for CML? Several claims contain phrases directed to staining patterns such as claims 13 and 14 but even those

claims lack a step that is specifically directed to deciding what is diagnostic for CML. For example, claim 13 produces a "distinctively altered" staining pattern but does not contain a step directed to then diagnosing CML. Claim 16 cites the phrase "relatively close" in line 11. Does this mean that a translocation is being detected? Doesn't BCR-ABL fusion require that the genes be visually directly connected on a translocated chromosome portion and not just proximal? Clarification is requested as to what diagnostic practice is meant to be included within the scope of the above rejected claims.

Claims 11, 13-15, and 53 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Claim 11 does not further limit claim 10 from which it depends because there are no added method step limitations in said claim 11, but rather only lists different results that are possible from the practice of the method of claim 10 which is identical for either claim 10 or 11. Similarly claims 13-15 are not further limiting from claim 12 since no added method step limitations are therein cited but rather only particular results of the practice of the claimed method which is identical for any of claims 12-15.

Claim 53 cites what the method of claim 10 is useful for but does not cite any added method step limitations and is therefore not further limiting from claim 10.

Claims 10-15, 17-19, 53, 129, and 130 are rejected under 35

U.S.C. § 102(b) as being clearly anticipated by Yunis et al.

Yunis et al. discloses in situ hybridization to metaphase human chromosomal DNA in the abstract on page 335 and on page 336, last two paragraphs. The preparation of labeled DNA probes from total cytoplasmic RNA is given on page 336 in the sections entitled "Isolation of Poly(A)-rich RNA" and "Synthesis of cDNA". The disabling of repetitive sequences during said hybridization is given on page 337 in the section entitled "Competition Experiments Using Total Repetitive DNA". Results of this competition procedure is given in the bridging paragraph between pages 341-342. The disclosure of Yunis et al. reads on the above rejected claims also since the in situ hybridization is human chromosome-specific and includes all of the human chromsomes which is clearly more than 35 kilobases in complexity as well as complexity inclusive of 1 megabase as given in instant claim 17. It is noted that the disclosure of Yunis et al. is not directed to CML diagnosis but that the instant claims are indistinguishable from Yunis et al. because nothing in the method steps of the instant claims limits the hybridization practice to CML diagnosis and certainly not the use of high complexity probes. The citation in the preamble of claim 10, lines 6-9, are not deemed to be claimed method steps because these lines disclose a possible result of the claimed method but not actual method steps. This lack of distinguishing limitations causes Yunis et al. to read on the instant claims.

Claims 10-15, 17-19, 53, 128, and 130 are rejected under 35

U.S.C. § 102(b) as being clearly anticipated by Olsen et al.

Olsen et al. reads on the above claims with regard to the methods disclosed therein, especially given on page 2422 in Figure 1 with associated description in the section entitled "Experimental Procedures". The labeled human X chromosome preparation of Olsen et al. is freed of repetitive nucleic acids as well as human X chromosome specific as well as directed to unique nucleic acid fragments. The human X chromosome has a complexity well above either 35 kilobases or 1 megabase as the instantly claimed limits to target complexity. This is thus a species of the instant generic claims. A prior art species clearly anticipates a generic claim. The use of this reference to base the above rejection on is permitted by the lack of distinguishing method step limitations as also discussed above regarding Yunis et al.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same

person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 10, 11, 17-19, 51, and 53 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Weissman et al.

The instant invention is directed to the method of staining of chromosomal DNA using high complexity probe mixtures with a complexity as high as 1 megabase. CML diagnostic limitations are not present in the instantly claimed method steps as noted above.

The basis for the § 102(e) rejection is given first as follows:

Weissman et al. discloses the composition of a mixture of nucleic acid segments covering a long section of chromosome including preparation from disease or clearly abnormal chromosomal source material, see column 8, lines 9-30. The complexity of the nucleic acids represented in the mixture is cited by Weissman et al. as being over 35 kilobases in that column 8, lines 41-45, cites 50 kilobases and greater. Weissman et al. extends the possible size of chromosomal coverage up to 2,000 kilobases as given in column 9, lines 14-32. The upper limit appears to depend on the ability to fractionate the

segments prior to the circularizing step used by Weissman et al. Weissman et al. discloses various labels including biotin labelling of probes in column 11, lines 45, through column 12, line 7. The uniqueness of the probe segments of Weissman et al. is disclosed as "single-copy" gene probes in column 7, line 64, through column 8, line 6. Weissman et al. discloses the importance of the "single-copy" characteristic of the probes with alternative ways of achieving this in column 14, line 46, through column 15, line 25. Note the disclosure in column 15, lines 21-22, wherein the clones are "screened for single-copy inserts". The cloning of the probes is disclosed in column 15, lines 26-30. The hybridization of a mixture of nucleic acids to a complex region of chromosome is disclosed in Figure 5 along with associated description given in column 18, lines 47-62. These disclosures read on the instant in-situ hybridization claims wherein disabling of repetitive fragments is performed by preventing their inclusion in the probe mixture.

Secondly, the basis for the § 103 rejection is as follows:

The disclosure of Weissman et al. reads on the instant claims as given above but may lack a clear definition of "repetitive" sequences and their removal but rather focuses its method and compositions on single-copy sequences. Also Weissman et al. lacks specific disclosure of some of the specific diseases such as CML. The disclosure of "single-copy" sequences by Weissman et al. is deemed to obviously suggest the removal or freeing of probes disclosed therein of repetitive sequence

motivated by the preparation and use of "single-copy" probe sequences. Also the general discussion of genetic rearrangement diseases as given in column 7, line 64, through column 8, line 30, suggests and motivates the application of this technique to other diseases such as CML. Thus it would have been obvious at the time of the instant invention to practice the instant invention using probe lacking repetitive sequences as well as directed to a multitude of diseases arising from genetic rearrangements because Weissman et al. supplies general motivation to practice both elements of the instant claims as well as the basis compositions and procedures of the instant claims especially since the instant claims also do not contain limitations clearly directing the invention to specific methods for CML diagnosis.

Claims 10, 11, 17-19, 51, 53, 128, and 130 are rejected under 35 U.S.C. § 103 as being unpatentable over Weissman et al. taken in view of Sealey et al.

The invention is directed to the preparation and use in in situ hybridization of complex probe mixtures where the repetitive nucleic acids have been removed by preassociation with total human DNA.

The disclosure of Weissman et al. has been summarized above with regard to compositions and hybridization methods. This disclosure lacks the removal of repetitive sequences by preassociation with total genomic DNA or the removal of said sequences by Cot fractionation. Weissman et al. supplies

motivation to use prior art techniques for said removal in column 15, lines 18-22, wherein convention cloning techniques are suggested for screening for single-copy clones.

Sealey et al. discloses the both the competitive inclusion of repetitive sequences in the cloned probe mixtures and the removal via Cot fractionation either in solution or using bound competitor on various solid supports in the last two paragraphs on page 1906.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to use the conventional technique of Sealey et al. with the in situ hybridization technique of Weissman et al. to practice the instant invention because Weissman et al. motivates the combination of these two disclosures.

Claims 10-12 and 127-130 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51, 112, and 114 of copending application Serial No. 07/627,707. Although the conflicting claims are not identical, they are not patentably distinct from each other because of reasons already summarized in a previous office action mailed 7/28/92 in the parent application 07/537,305 to the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is a

judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

The reference by Montgomery et al. is cited of interest in the instant application.

The disclosure is objected to because of the following informalities:

On page 19, line 5, the word "earrangement" appears to be misspelled.

On page 31-33, the sections of Figure 11 are discussed. This discussion of Figure 11 is however confusing in that the sections are denoted on pages 31-33 by the use of uncapitalized letters whereas the Figure 11 drawings use capitalized letters to denote each section. Clarification is requested that makes the letter designations uniform as to capitalization or not.

On page 58, line 11, the word "Labora- tories" is awkwardly hyphenated.

Appropriate correction is required.

Claims 16, 51, and 52 are allowable over the prior art of record because hybridization detection via different probe labeling for BCR versus ABL regions for detection of BCR-ABL fusion using high complexity hybridization probes including prognostic and/or determination of the effectiveness of therapy is neither taught nor suggested by the prior art of record.

No claim is allowed.

Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 308-4227 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

AM

A. MARSCHEL:am

July 12, 1993

MARGARET MOSKOWITZ PAEN
SUPERVISORY PATENT EXAMINER
GROUP 180